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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/403,539	10/22/99	DEAN N	ISIS-3013

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EXAMINER	
SHIBUYA,M	
ART UNIT	**PAPER NUMBER**
1635	7

DATE MAILED: 10/18/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

FILE

Office Action Summary	Application No. 09/403,539	Applicant(s) DEAN ET AL.
	Examiner Mark L. Shibuya	Group Art Unit 1635

☒ Responsive to communication(s) filed on *Sep 25, 2000*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1, 8, 10-18, and 27-33* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 8, 10-18, and 27-33* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5, 6*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Priority

1. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

Information Disclosure Statement

2. The information disclosure statement filed 4/24/2000 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information citing publications for which no copy has been provided by the applicant, referred to therein, has not been considered.

a. No copies have been furnished of applicant's references: AE, AG, AH , AI, AO, AS AT, AU, BA, BM, BX, CD, CE, CF, CG, CH, CI, CK, CS, CV, CW, CZ, DD, DF, DJ, DN, DO, DR, DS, DT, DV, DX, DY, EA, EB, ED, EE, EF, EI, EJ, EK, EM, EP, EQ, and EV.

Specification

3. The disclosure is objected to because of the following informalities: The specification at, *e.g.*, p. 20, lines 11, 13 and 25, p. 21, line 3, p. 23, line 12 and 3, p. 24, line 4 and p. 27, line 8,

recites "United States patent X,XXX,XXX", however reference to US Patents must include their actual number.

Appropriate correction is required.

Double Patenting

4. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

5. Applicant is advised that should claim 28 be found allowable, claim 30 will be objected to under 37 CFR 1.75 as being a duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 1, 8 and 10 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 5,789,573 (filed 5/24/96). Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-4 of the '573 patent are drawn to antisense oligonucleotides, which target ICAM gene expression, and comprising a heteroatomic backbone of methylene(methylimino) ("MMI"), peptide-nucleic acid or morpholino groups, further comprising at least one 2' alkoxyalkoxy sugar modification that is 2'-methoxyethoxy. Claims 1-4 of the '573 patent therefore constitute a species of the genus of antisense oligonucleotides comprising a nitrogenous heteroatomic backbone of methylene(methylimino) ("MMI"), peptide-nucleic acid or morpholino groups, further comprising at least one 2' sugar modification wherein said 2' sugar modification is 2'-alkoxyalkoxy and wherein said 2'-alkoxyalkoxy is 2'-methoxyethoxy, as in claims 1, 8 and 10 of the instant application. Because a genus is not patentably distinct from its species, claims 1, 8 and 10 are not patentably distinct from claims 1-4 of U.S. Patent No. 5,789,573.

8. Claims 1, 8 and 10 are directed to an invention not patentably distinct from claims 1-4 of commonly assigned U.S. Patent No. 5,789,573 ('573 patent). Specifically, claims 1-4 of the '573

patent are drawn to antisense oligonucleotides, which target ICAM gene expression, and have methylene(methylimino) backbone modifications and 2' sugar modification, and so claim a species of the genus of antisense oligonucleotides that have methylene(methylimino) backbone modifications and 2' sugar modification, as in claims 1, 8 and 10 of the instant application. Because a genus is not patentably distinct from its species, claims 1, 8 and 10 are not patentably distinct from claims 1-4 of U.S. Patent No. 5,789,573.

a. Commonly assigned U.S. Patent No. 5,789,573, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 CFR 1.78(c) and 35 U.S.C. 132 to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

b. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g). *See below* rejection under 35 U.S.C. 102 (f) or (g)/103.

9. Claims 10-16 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 5,789,573 in view of Milligan et al., Kahne, (U.S. Patent No. 5,795,870), and Carrano et al., (U.S. Patent No. 5,739,118).

a. Claims 1-4 of the '573 patent are drawn to antisense oligonucleotides, which target ICAM gene expression, and comprising a heteroatomic backbone of methylene(methylimino) ("MMI"), peptide-nucleic acid or morpholino groups, further comprising at least one 2' alkoxyalkoxy sugar modification that is 2'-methoxyethoxy.

b. **Milligan et al.** (Journal of Medicinal Chemistry, July 1993, Vol. 36, No. 14, pp. 1923-1937), at p. 1923, Table 1 and p. 1931, para 2, Figure 3, and p. 1932, para 5 to 1933, para 1, teach modified oligonucleotides comprising at least one nitrogenous heteroatomic backbone modification, including methylene(methylimino) linkages, in order to impart stability and enhance affinity and cellular permeation; modified oligonucleotides comprising at least one 2' sugar modification in order to enhance stability and affinity, and wherein said oligonucleotides also comprise a backbone modification; and oligonucleotides comprising 5'-methylcytidine in order to enhance the stability of hybridization.

c. **Carrano et al., U.S. Patent No. 5,739,118,** at col. 3, lines 26-62, col. 11, lines 58-67, col. 12, lines 1-13 and 63-67, col. 13, lines 1-13 and lines 54-67, col. 14, lines 1-22, teach compositions for the therapeutic administration of nucleic acid molecules, including antisense oligonucleotides, comprising penetration enhancers that are fatty acids, which include sodium laurate, for the preparation of pharmaceutical compositions that are emulsions in colloidal

dispersion systems, wherein the pharmaceutical compositions are delivered orally or by suppository, *i.e.*, into the alimentary canal. As the reference of Carrano et al. discloses, the sodium laurate facilitates uptake of genetic material by the cells.

d. **Kahne, U.S. Patent No. 5,795,870,** at col. 4, lines 25-59, disclose compositions for the therapeutic administration of nucleic acid molecules, including antisense oligonucleotides, comprising fatty acids and bile salts, including chenodeoxy cholic acid (CDCA), for enhancing the uptake of nucleic acids to genetically transform cells.

e. It would have been prima facie obvious at the time the invention was made to one of ordinary skill in the art to make and use a modified oligonucleotide comprising at least one heteroatomic backbone modification and a 2'-alkoxyalkoxy modification, pharmaceutical compositions thereof that comprises a colloidal dispersion system, or a penetration enhancer that is a bile salt and is CDCA (chenodeoxy cholic acid), or that is a fatty acid and is sodium laurate, or both a bile salt and a fatty acid; and a pharmaceutical composition comprising an oligonucleotide having, *i.e.*, comprising, an oligonucleotide comprising at least one 2'-alkoxyalkoxy modification that is 2'-methoxyethoxy and at least one 5-methylcytidine.

f. One of ordinary skill in the art would have had been motivated to further modify oligonucleotides comprising 2'-methoxyethoxy modifications with heteroatomic backbone modifications that are methylene(methylimino) or methylcytidine, because said oligonucleotide modifications, including the 2' methoxyethoxy modifications, are employed to enhance affinity and cellular permeation, as taught by Milligan et al. One of ordinary skill in the art would have

been motivated to make and use pharmaceutical composition comprising modified oligonucleotides with at least one heteroatomic backbone modification and a 2'-alkoxyalkoxy modification and further comprising a colloidal dispersion system, or a penetration enhancer that is a bile salt and is CDCA (chenodeoxy cholic acid), or that is a fatty acid and is sodium laurate, or both a bile salt and a fatty acid, because a colloidal dispersion system, and bile salt or fatty acid penetration enhancers that are bile salts or fatty acids sodium laurate, are "necessities", as taught by Carrano et al., at col. 14, lines 6-25, for the preparation of pharmaceutical compositions that are emulsions in colloidal dispersion systems, wherein the pharmaceutical compositions are delivered orally or by suppository, *i.e.*, into the alimentary canal as taught by Carrano; and for facilitating the uptake of genetic material by the cells, as taught by Kahne.

10. Claims 17 and 18 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 5-7 of U.S. Patent No. 6,087,489 (filed 6/2/98). Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1 and 5-7 of the '489 patent are drawn to antisense oligonucleotides, which target human thymidylate synthase gene expression, and comprising at least one 2'-alkoxyalkoxy modification that is 2'-methoxyethoxy (also known as 2'-O-methoxyethyl) and at least one 5-methylcytidine. Claims 1 and 5-7 of the '489 patent therefore constitute a species of the genus of antisense oligonucleotides comprising at least one 2'-alkoxyalkoxy modification that is 2'-methoxyethoxy and at least one 5-methylcytidine, as in claims 17 and 18 of the instant

application. Because a genus is not patentably distinct from its species, claims 17 and 18 of the instant application are not patentably distinct from claims 1 and 5-7 of U.S. Patent No. 6,087,489.

11. Claims 17 and 18 are directed to an invention not patentably distinct from claims 1 and 5-7 of commonly assigned U.S. Patent No. 6,087,489 ('489 patent). Specifically, claims 1 and 5-7 of the '489 patent are drawn to antisense oligonucleotides, which target human thymidylate synthase gene expression, comprising at least one 2'-alkoxyalkoxy modification that is 2'-methoxyethoxy (also known as 2'-O-methoxyethyl) and at least one 5-methylcytidine, and so claim a species of the genus of antisense oligonucleotides comprising at least one 2'-alkoxyalkoxy modification that is 2'-methoxyethoxy (also known as 2'-O-methoxyethyl) and at least one 5-methylcytidine, as in claims 17 and 18 of the instant application. Because a genus is not patentably distinct from its species, claims 17 and 18 are not patentably distinct from claims 1 and 5-7 of U.S. Patent No. 6,087,489.

a. Commonly assigned U.S. Patent No.6,087,489, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 CFR 1.78(c) and 35 U.S.C. 132 to either show that the conflicting inventions were commonly owned at the time the invention in this application was

made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

b. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g). *See below* rejection under 35 U.S.C. 102 (f) or (g)/103.

12. Claims 27, 28, 30, 31, 32, and 33 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 21 and 28-32 of copending Application No. 08/847,151. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claimed methods of the instant application drawn to modulating expression of a target nucleic acid comprising administering into the alimentary canal an oligonucleotide that has at least one nitrogenous heteroatomic backbone modification and hybridizes to said target nucleic acid; wherein the oligonucleotide has a 2'-O-alkyl or 2'-alkoxyalkoxy modification, wherein said 2'-O-alkyl modification is a 2'-O-methyl or 2'-O-propyl modification, and wherein said 2'-alkoxyalkoxy modification is a 2'-methoxyethoxy modification, **encompasses** the claimed methods of copending Application No.08/847,151, drawn to modulating expression of a target nucleic acid comprising administering into the alimentary canal, an oligonucleotide that has at least one nitrogenous heteroatomic backbone modification and hybridizes to said target nucleic acid, *and which has enhanced bioavailability compared to a*

phosphorothioate oligonucleotide; wherein the oligonucleotide has a 2'-O-alkyl or 2'-alkoxyalkoxy modification, wherein said 2'-O-alkyl modification is a 2'-O-methyl or 2'-O-propyl modification, and wherein said 2'-alkoxyalkoxy modification is a 2'-methoxyethoxy modification.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

13. Claim 29 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 21 of copending Application No. 08/847,151, in view of Milligan.

a. Claim 29 of the instant application is drawn to methods for modulating expression of a target nucleic acid comprising administering into the alimentary canal an oligonucleotide that has at least one nitrogenous heteroatomic backbone modification and hybridizes to said target nucleic acid and wherein said nitrogenous, heteroatomic backbone modification is a methylene(methylimino) modification.

b. Claim 21 of copending Application No. 08/847,151 is drawn to methods for modulating expression of a target nucleic acid comprising administering into the alimentary canal, an oligonucleotide that has at least one nitrogenous heteroatomic backbone modification and hybridizes to said target nucleic acid, and which has enhanced bioavailability compared to a phosphorothioate oligonucleotide.

c. Milligan et al., *Current Concepts in Antisense Drug Design*, J. Medicinal Chemistry 36 (14) 1923 (1993), at p. 1923, Table 1 and p. 1931, Figure 3 teach oligonucleotides comprising a heteroatomic backbone modification that is a methylene(methylimino) modification.

d. It would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to have used methods for modulating expression of a target nucleic acid comprising administering into the alimentary canal an oligonucleotide that has at least one nitrogenous heteroatomic backbone modification and hybridizes to said target nucleic acid and wherein said nitrogenous, and wherein the heteroatomic backbone modification is a methylene(methylimino) modification. One of ordinary skill in the art would have been motivated to use a heteroatomic backbone modification that is a methylene(methylimino) modification because the reference of Milligan et al., at pp. 1931-33, teaches that heteroatomic backbone modifications that are methylene(methylimino) modifications will increase the stability and cellular uptake of antisense oligonucleotides.

This is a provisional obviousness-type double patenting rejection.

Claim Rejections - 35 U.S.C. § 112

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 27-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of modulating expression of a target nucleic acid comprising administering into the alimentary canal an effective amount of an oligonucleotides comprising 2'-O-alkyl or 2'-O-alkoxy modifications, does not reasonably provide enablement for methods of inhibiting gene expression by the oral administration of oligonucleotides that do not comprise 2'-O-alkyl or 2'-O-alkoxy modifications. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

a. Claims 27-30 are drawn broadly to a method of modulating expression of a target nucleic acid comprising administering into the alimentary canal an effective amount an oligonucleotide comprises at least one nitrogenous heteroatomic backbone modification and hybridizes to said target nucleic acid. The claims, when given their broadest reasonable interpretation, encompass *in vivo* methods comprising oligonucleotides that do not comprise 2'-O-alkyl or 2'-O-alkoxy modifications.

b. The specification provides examples of administration by intraduodenal instillation, wherein a catheter is inserted through the abdominal wall, into and out of the stomach, past the pylorus and into the duodenum (specification at p. 31, line 12 to p. 32, line 16, examples 2 and 3). The specification, at p. 21, line 26 to p. 22, line 11, discloses compositions for oral administration including "powders, granules, suspensions or solutions in water or non-aqueous media, capsules, sachets, troches, tablets or SECs (soft elastic capsules or 'caplets') . . . [t]hickeners, flavoring

agents, diluents, emulsifiers, dispersing aids, carrier substances or binders". The specification further contemplates oligonucleotides as antisense oligonucleotides comprising modification nitrogenous heteroatomic backbone modifications. The specification refers to oral bioavailability in Figures 2 and 4 of the instant application, but provides no direction or guidance as to the conditions and procedures of oral administration.

c. It is known in the art that under highly acidic conditions, such as those found in the digestive environment of the stomach, oligonucleotides will undergo depurination. It is also known in the art that this depurination may be resisted by modifications to the 2' position of the the nucleosidic sugar ring, in particular, the 2'-O-methyl modification.

d. The specification does not provide particular guidance or particular direction for the administration of oligonucleotides throughout the alimentary tract, including rectal, sublingual/buccal, or the most preferred, oral administration and does not provide a nexus between intraduodenal administration, which bypasses the acidic digestive environment of the gastric juices of the stomach, and other alimentary canal routes, most particularly oral administration. The specification does not disclose that oligonucleotides comprising nitrogenous heteroatomic modifications, or other modifications, would resist the acidic conditions found in the stomach, although it is known in the art that oligonucleotides comprising 2' sugar modifications, resist depurination under highly acidic conditions. Therefore there it is unpredictable that there will be sufficient intact oligonucleotide, wherein the oligonucleotide does not comprise a 2'-sugar modification, to modulate gene expression. The instant application offers no guidance as to the

delivery of any amount of antisense oligonucleotides into cells sufficient to give an antisense effect *in vivo*. The instant application provides no particular guidance or particular direction that a oligonucleotide comprising a nitrogenous heteroatomic backbone modification would be acid resistant.

e. Simon et al., U.S. Patent No. 6,005,094, at col. 1, lines 18-53, col. 2, lines 5-15, teach modification of the 2' position on the sugar moiety of nucleosidyl units in order to avoid depurination due to the acidic conditions of the stomach. Simon et al. teach oligonucleotides that have a 2'-O-alkyl modification that is an 2'-O-methyl modification. Simon et al. state:

> The oral delivery of therapeutic oligodeoxyribonucleotides may require exposure of the drug to the acidic conditions of the stomach (about pH 1) for up to about 4 hours under normal conditions of drug delivery and under conditions of sustained released drug delivery (see, e.g., U.S. Patent No. 4,839,177), for up to about 12 hours. Due to its lack of stability under acid conditions, it is unlikely that enough of an orally administered oligodeoxynucleotide would remain intact to be effective. Ribonucleic acid (RNA) has been reported to be significantly more stable to depurination under acidic conditions than its DNA counterpart reportedly because of the apparent stabilizing effect of the 2' [hydroxyl] on the glycosidic bond between sugar and the base . . . .

Simon et al., U.S. Patent No. 6,005,094, at col. 1, lines 27-41.

f. Furthermore, Agrawal et al., *Absorption, Tissue Distribution and In Vivo Stability in Rats of a Hybrid Antisense Oligonucleotide Following Oral Administration*, Biochemical Pharmacology 50 (4), 571-576 (1995) at p. 573, para 5, states that HPLC analysis of portal venous blood, systemic plasma, and various tissues following oral administration of antisense oligonucleotides, demonstrated the presence of both intact and degraded products.

g. Oral administration of oligonucleotides is unpredictable. For example applicants' ref. BS (Robertson, IDS filed 4/24/2000) at p. 209, last paragraph, states: "In one sense, some critics would argue, the recent ISIS trial changes nothing: The pharmacokinetic properties of antisense have always been predicable--'predictably bad'--with limited stability and oral availability."

h. Rojanasakul, *Antisense oligonucleotide therapeutics: drug delivery and targeting*, Advanced Drug Delivery Reviews v. 18, 115-131 (1996) at p. 118-19, teaches that delivery of antisense oligonucleotides into cells must overcome problems with delivery, that antisense oligonucleotides are subject to enzymatic degradation once inside the cells, that the antisense must locate and specifically bind to its intended target in order to inhibit expression of the disease-causing gene, and that the art is unpredictable and at an early stage of development.

i. Nicklin et al., Pharmaceutical Research, April 1998, Vol. 15, No. 4, pp. 583-591, in comparing bioavailability of oligonucleotides administered through different routes, at p. 589, finds that although oral administration combines clinical convenience with patient acceptability, "the implicit requirement for efficient transepithelial tranport, however presents a formidable challenge for antisense oligonucleotides. Nicklin et al., found that "the oral route is not feasible for phosphorothioate oligodexoxynucleotides. While noting that Agrawal et al. reported the oral bioavailability of a hybrid oligonucletide with a uniform phosphorothioate backbone and additional 2-O-methyl modifications, "[b]ecause of clear discrepancies between different workers and its potential importance to the field, we are currently defining the absolute oral bioabailability for several chemically modified oligonucleotides in a variety of animal species"..

j. *De novo* experimentation would be required to show that oligonucleotide not comprising 2' sugar modifications administered orally would resist depurination in quantities sufficient to modulate the gene expression within a cell in the whole organism. *De novo* experimentation would be required of the practitioner to administer oligonucleotides by any alimentary tract route, as is broadly claimed, because the alimentary tract contains many different environments, functions in many different capacities, and is formed by many different structure, so that administration by one route through the alimentary tract would not be enabling for all other routes through the alimentary tract. The specification does not provide adequate disclosure for claims broadly drawn to the administration of oligonucleotides throughout the alimentary tract, including rectal, sublingual/buccal, or oral administration. Therefore it would require undue experimentation on the part of one of skill in the art to practice the claimed invention.

Claim Rejections - 35 U.S.C. § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

17. Claims 1, 8 and 10 are rejected under 35 U.S.C. 102(e) as being anticipated by Baker et al., U. S. Patent No. 5,789,573. *See above* rejection under Double Patenting.

18. The applied reference has a common assignee and at least one common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by a showing of a date of invention for the instant application of any unclaimed subject matter prior to the effective U.S. filing date of the reference under 37 CFR 1.131.

a. Claims 1, 8 and 10 are drawn to antisense oligonucleotides comprising a nitrogenous heteroatomic backbone of methylene(methylimino) ("MMI"), peptide-nucleic acid or morpholino groups, further comprising at least one 2' sugar modification wherein said 2' sugar modification is 2'-alkoxyalkoxy and wherein said 2'-alkoxyalkoxy is 2'-methoxyethoxy.

b. Baker et al. (U.S. Patent No. 5,789,573), at claims 1-4 (*see above* rejections under Double Patenting), col. 2, lines 40-64 and col. 3, line 57 to col. 4, line 30, disclose oligonucleotides comprising at least one heteroatomic backbone modification, wherein said nitrogenous heteroatomic backbone is methylene(methylimino) ("MMI"), peptide-nucleic acid or morpholino, and further comprising at least one 2' sugar modification wherein said 2' sugar modification is 2'-alkoxyalkoxy and wherein said 2'-alkoxyalkoxy is 2'-methoxyethoxy. Absent evidence to the contrary, the oligonucleotide comprising at least 2'-alkoxyalkoxy taught by Baker et al. would inherently have enhanced bioavailability compared to a phosphorothioate oligodeoxynucleotide of substantially the same sequence.

c. Because Baker et al. disclose a species of the genus of antisense oligonucleotides of claims 1, 8 and 10 of the instant application and because a genus is anticipated by a species, said claims 1, 8 and 10 are anticipated by Baker et al. (U.S. Patent No. 5,789,573).

19. Claims 17 and 18 are rejected under 35 U.S.C. 102(e) as being anticipated by Dean, U. S. Patent No.6,087,489. *See above* rejection under Double Patenting.

20. The applied reference has a common assignee and at least one common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by a showing of a date of invention for the instant application of any unclaimed subject matter prior to the effective U.S. filing date of the reference under 37 CFR 1.131.

a. Claims 17 and 18 are drawn to antisense oligonucleotides comprising at least one 2'-alkoxyalkoxy modification that is 2'-methoxyethoxy and at least one 5-methylcytidine.

b. Dean (U.S. Patent No.6,087,489), at claims 1 and 5-7 (*see above* rejections under Double Patenting), col. 9, lines 7-11, 32-34, and 60-67, col. 19, lines 17-21, col. 20, lines 7-17, Tables 1 and Table 2, disclose oligonucleotides which target human thymidylate synthase gene expression, and comprising at least one 2'-alkoxyalkoxy modification that is 2'-methoxyethoxy (also known as 2'-O-methoxyethyl) and at least one 5-methylcytidine.

c. Because Dean et al. disclose a species of the genus of antisense oligonucleotides of claims 17 and 18 of the instant application and because a genus is anticipated by a species, claims 17 and 18 are anticipated by Dean (U.S. Patent No.6,087,489).

21. Claims 1, 8 and 10 are rejected under 35 U.S.C. 102(f)/(g) as being anticipated by Baker et al., U. S. Patent No. 5,789,573. *See above* rejection under Double Patenting.

a. Claims 1, 8 and 10 are drawn to antisense oligonucleotides comprising a nitrogenous heteroatomic backbone of methylene(methylimino) ("MMI"), peptide-nucleic acid or morpholino groups, further comprising at least one 2' sugar modification wherein said 2' sugar modification is 2'-alkoxyalkoxy and wherein said 2'-alkoxyalkoxy is 2'-methoxyethoxy.

b. Baker et al. (U.S. Patent No. 5,789,573), at claims 1-4 (*see above* rejections under Double Patenting), col. 2, lines 40-64 and col. 3, line 57 to col. 4, line 30, disclose oligonucleotides comprising at least one nitrogenous heteroatomic backbone modification, wherein said nitrogenous heteroatomic backbone is methylene(methylimino) ("MMI"), peptide-nucleic acid or morpholino, and further comprising at least one 2' sugar modification wherein said 2' sugar modification is 2'-alkoxyalkoxy and wherein said 2'-alkoxyalkoxy is 2'-methoxyethoxy.

c. Because Baker et al. disclose a species of the genus of antisense oligonucleotides of claims 1, 8 and 10 of the instant application and because a genus is anticipated by a species, claims 1, 8 and 10 are anticipated by Baker et al. (U.S. Patent No. 5,789,573).

22. Claims 17 and 18 are rejected under 35 U.S.C. 102(f)/(g) as being anticipated by 17 and 18 are anticipated by Dean (U.S. Patent No.6,087,489). *See above* rejection under Double Patenting.

a. Claims 17 and 18 are drawn to antisense oligonucleotides comprising at least one 2'-alkoxyalkoxy modification that is 2'-methoxyethoxy and at least one 5-methylcytidine.

b. Dean (U.S. Patent No.6,087,489), at claims 1 and 5-7 (*see above* rejections under Double Patenting), col. 9, lines 7-11, 32-34, and 60-67, col. 19, lines 17-21, col. 20, lines 7-17, Tables 1 and Table 2, disclose oligonucleotides which target human thymidylate synthase gene expression, and comprising at least one 2'-alkoxyalkoxy modification that is 2'-methoxyethoxy (also known as 2'-O-methoxyethyl) and at least one 5-methylcytidine.

c. Because Dean et al. disclose a species of the genus of antisense oligonucleotides of claims 17 and 18 of the instant application and because a genus is anticipated by a species, claims 17 and 18 are anticipated by Dean (U.S. Patent No.6,087,489).

Claim Rejections - 35 U.S.C. § 103

23. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to

the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

24. Claims 1, 8, and 10-18 rejected under 35 U.S.C. 103(a) as being unpatentable over Hanecak et al., in view of Milligan et al., Kahne, (U.S. Patent No. 5,795,870), and Carrano et al., (U.S. Patent No. 5,739,118).

a. **Hanecak et al.** (Journal Of Virology, Aug. 1996, Vol. 70, No. 8, pp. 5203-5212), at p. 5204, para 3, 5208, para 1, teach oligonucleotides comprising 2'-alkoxyalkoxy modifications that are 2'-methoxyethoxy modifications in order to increase nuclease resistance and hybridization affinity.

b. Hanecak et al. do not teach a modified oligonucleotide comprising at least one heteroatomic backbone modification and a 2'-alkoxyalkoxy modification, pharmaceutical compositions thereof that comprise a colloidal dispersion system, a penetration enhancer that is a bile salt that is CDCA (chenodeoxy cholic acid), or a fatty acid that is sodium laurate, or both; and a pharmaceutical composition comprising an oligonucleotide having, *i.e.*, comprising, an oligonucleotide comprising at least one 2'-alkoxyalkoxy modification that is 2'-methoxyethoxy and at least one 5-methylcytidine.

c. **Milligan et al.** (Journal of Medicinal Chemistry, July 1993, Vol. 36, No. 14, pp. 1923-1937), at p. 1923, Table 1 and p. 1931, para 2, Figure 3, and p. 1932, para 5 to 1933, para 1, teach modified oligonucleotides comprising at least one nitrogenous heteroatomic backbone

modification, including methylene(methylimino) linkages, in order to impart stability and enhance affinity and cellular permeation; modified oligonucleotides comprising at least one 2' sugar modification in order to enhance stability and affinity, and wherein said oligonucleotides also comprise a backbone modification; and oligonucleotides comprising 5'-methylcytidine in order to enhance the stability of hybridization.

d. **Carrano et al., U.S. Patent No. 5,739,118**, at col. 3, lines 26-62, col. 11, lines 58-67, col. 12, lines 1-13 and 63-67, col. 13, lines 1-13 and lines 54-67, col. 14, lines 1-22, teach compositions for the therapeutic administration of nucleic acid molecules, including antisense oligonucleotides, comprising penetration enhancers that are fatty acids, which include sodium laurate, for the preparation of pharmaceutical compositions that are emulsions in colloidal dispersion systems, wherein the pharmaceutical compositions are delivered orally or by suppository, *i.e.*, into the alimentary canal. As the reference of Carrano et al. discloses, the sodium laurate facilitates uptake of genetic material by the cells.

e. **Kahne, U.S. Patent No. 5,795,870,** at col. 4, lines 25-59, disclose compositions for the therapeutic administration of nucleic acid molecules, including antisense oligonucleotides, comprising fatty acids and bile salts, including chenodeoxy cholic acid (CDCA), for enhancing the uptake of nucleic acids to genetically transform cells.

f. It would have been prima facie obvious at the time the invention was made to one of ordinary skill in the art to make and use a modified oligonucleotide comprising at least one nitrogenous heteroatomic backbone modification and a 2'-alkoxyalkoxy modification,

pharmaceutical compositions thereof that comprises a colloidal dispersion system, or a penetration enhancer that is a bile salt and is CDCA (chenodeoxy cholic acid), or that is a fatty acid and is sodium laurate, or both a bile salt and a fatty acid; and a pharmaceutical composition comprising an oligonucleotide having, *i.e.*, comprising, an oligonucleotide comprising at least one 2'-alkoxyalkoxy modification that is 2'-methoxyethoxy and at least one 5-methylcytidine.

g. One of ordinary skill in the art would have had been motivated to further modify oligonucleotides comprising 2'-methoxyethoxy modifications with nitrogenous heteroatomic backbone modifications that are methylene(methylimino) or methylcytidine, because said oligonucleotide modifications, including the 2' methoxyethoxy modifications, are employed to enhance affinity and cellular permeation, as taught by Hanecak et al. and Milligan et al. One of ordinary skill in the art would have been motivated to make and use pharmaceutical composition comprising modified oligonucleotides with at least one nitrogenous heteroatomic backbone modification and a 2'-alkoxyalkoxy modification and further comprising a colloidal dispersion system, or a penetration enhancer that is a bile salt and is CDCA (chenodeoxy cholic acid), or that is a fatty acid and is sodium laurate, or both a bile salt and a fatty acid, because a colloidal dispersion system, and bile salt or fatty acid penetration enhancers that are bile salts or fatty acids sodium laurate, are "necessities", as taught by Carrano et al. at col. 14, lines 6-25, for the preparation of pharmaceutical compositions that are emulsions in colloidal dispersion systems, wherein the pharmaceutical compositions are delivered orally or by suppository, *i.e.*, into the

alimentary canal as taught by Carrano; and for facilitating the uptake of genetic material by the cells, as taught by Kahne.

25. Claims 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Simon et al., U.S. Patent No. 6,005,094, and further in view of Hanecak et al. and Milligan et al.

a. **Simon et al., U.S. Patent No. 6,005,094**, at col. 1, lines 18-53, col. 2, lines 5-15 and lines 36-42, col. 4, lines 15-25, col. 6, lines 9-67, col. 7, lines 1-53, teach methods of modulating expression of a target nucleic acid comprising administering into the alimentary canal an effective amount of an oligonucleotide that has a 2'-O-alkyl modification that is an 2'-O-methyl or a 2'-O-propyl modification and a heteroatomic backbone modification that is methylphosphonate. Simon et al. teach modification of the 2' position on the sugar moiety of nucleosidyl units in order to avoid depurination due to the acidic conditions of the stomach.

b. Simon et al. does not teach oligonucleotides comprising a nitrogenous heteroatomic backbone modification or a 2'-alkoxyalkoxy modification that is a 2'-methoxyethoxy modification.

c. **Milligan et al.** (Journal of Medicinal Chemistry, July 1993, Vol. 36, No. 14, pp. 1923-1937), at p. 1923, Table 1 and p. 1931, para 2, Figure 3, and p. 1932, para 5 to 1933, para 1, teach modified oligonucleotides comprising at least one nitrogenous heteroatomic backbone modification, including methylene(methylimino) linkages, in order to impart stability and enhance affinity and cellular permeation.

d. **Hanecak et al.** (Journal Of Virology, Aug. 1996, Vol. 70, No. 8, pp. 5203-5212), at p. 5204, para 3, 5208, para 1, teach oligonucleotides comprising 2'-alkoxyalkoxy modifications that are 2'-methoxyethoxy modifications in order to increase nuclease resistance and hybridization affinity.

e. It would have been *prima facie* obvious at the time the invention was made to one of ordinary skill in the art to use methods of modulating expression of a target nucleic acid comprising administering into the alimentary canal an effective amount of an oligonucleotide comprising at least one nitrogenous heteroatomic backbone modification and a 2'-O-alkyl modification that is a 2'-O-methyl or a 2'-O-propyl modification or a 2'-O-alkoxyalkoxy modification that is a 2'-methoxyethoxy modification.

f. One of ordinary skill in the art would have had been motivated to further modify oligonucleotide comprising 2'-alkyl modifications with nitrogenous heteroatomic backbone modifications that are methylene(methylimino), because said nitrogenous heteroatomic backbone modifications, are employed to enhance affinity and cellular permeation, Milligan et al. One of ordinary skill in the art would have been motivated to interchange 2'-alkoxyalkoxy modifications for 2'-alkyl modifications, because Simon et al. teach the alkylation of the 2' position of the nucleoside sugar moiety to avoid depurination in the highly acid environment of the stomach and because Hanecak et al. teach oligonucleotides comprising 2'-alkoxyalkoxy modifications that are 2'-methoxyethoxy modifications in order to increase nuclease resistance and hybridization affinity.

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mark L. Shibuya (SRC), Ph.D.*, whose telephone number is (703) 308-9355.

27. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *George Elliott, Ph.D.* may be reached at (703) 308-4003.

28. Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is (703) 308-0196.

Mark L. Shibuya
Patent Examiner
Technical Center 1600
October 7, 2000

ROBERT A. SCHWARTZMAN
PRIMARY EXAMINER